REMARKS

Of claims 1-44 which were contained in the original application, claims 1-15, drawn to a method of delivering a pharmaceutical through a membrane, and claims 43-44, drawn to a method of treating Gaucher's Disease (Group I claims), have been withdrawn from further consideration, as being drawn to non-elected inventions. Applicants reaffirm the election of claims 16-42 (Group II and Group III claims), with traverse. Claim 16-39 are drawn to a therapeutic phospholipid composition and claims 40-42 are drawn to a polypeptide.

It is noted that in paragraph 1 of the "Detailed Action" of July 2, 2003, the Examiner states that "Applicant's amendment of claims 11, 25, 37 and 42 in paper #17, filed May 1, 2003, is ***acknowledged***." It is understood by the Applicant that the intent of the Examiner was that these amendments to the claims have been ***entered*** and made of record. However, the Examiner makes no mention of the amendment to the specification presented in that same paper by the Applicant (paper #17). That being the case, this same amendment to the specification is being presented for a second time in this office action response. In addition, claims 40-42 are currently amended to incorporate the language "*consisting of* ". It should be noted that Applicant maintains that the original language of claims 40-42 is limiting in that these claims are directed to the given polypeptide sequences. However, in order to expedite prosecution of this case, the phrase "consisting of" has been added to these claims; these are not narrowing amendments. No new matter is being introduced as a result of these amendments. Finally, several claims have been amendedto correct typos and singular/plural language.; these are not intended to be narrowing amendments.

Before considering the rejections in detail, the fundamental concepts of the present invention will be briefly reviewed. The present invention comprises a composition and method for delivering a pharmaceutical agent through a biological membrane. The method comprises applying to a membrane a composition comprising anionic phospholipids, a safe and effective amount of a pharmaceutical agent contained within the phospholipids, and a fusogenic protein or polypeptide derived from prosaposin in a pharmaceutically acceptable carrier. The pharmaceutical agent contained within the liposome may comprise large biomolecules and/or small organic molecules. The membrane fusion protein is associated with the phospholipid membrane, through electrostatic and hydrophobic interactions. The targeted biological membranes include, but are not limited to, dermal membranes and mucosal membranes. This technology can be used for both cosmetic and medicinal applications in which the objective is delivery of the active agent within and/or beneath the dermal or mucosal membranes.

Rejections Under 35 U.S.C. §112, first paragraph

Claims 21, 26-29, and 33 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 21, 26-29 and 33 are directed to a composition comprising Saposin A, Saposin C or SEQ ID NOS. 1-6, as well as derivatives, homologues, fragments or analogs thereof. The Examiner maintains that the specification does not describe all derivatives, fragments, analogs or naturally occurring variants, or provide guidance regarding how to obtain specific derivatives, fragments, analogs or naturally occurring

variants that retain the function of the saposin protein. The language referring to derivatives, fragments, analogs or naturally occurring variants of saposin in claims 21, 28 and 33 has been deleted. Therefore, the rejection of claims 21, 26-29 and 33 has been rendered moot and it is respectfully requested that this rejection be withdrawn.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 17-27, 29, 31, 32, 34 37, 39 and 44 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention.

In making this rejection, the Examiner asserts that even though claims 17-27 recite the limitation "phospholipid composition" there is insufficient antecedent basis for this limitation since independent claim 16 recites "anionic phospholipids." The Examiner states that the Applicant can overcome this rejection by amending the claim to recite "anionic phospholipids." It is unclear as to what the Examiner intends since claim 16 recites "A *therapeutic phospholipid composition* comprising: (a) an *anionic phopholipid*...." and claim 17 is directed to "[t]he *phospholipid composition* of claim 16 wherein the concentration of *phospholipids*...." However, in an attempt to address this rejection, claim 17 has been amended to recite "[t]he <u>therapeutic</u> phospholipid composition of claim 16 wherein the concentration of <u>anionic</u> phospholipids...." In addition, claims 18-27 have also been amended to recite "The <u>therapeutic</u> phospholipid composition...".

The Examiner also maintains that while claim 29 recites the limitation "phospholipid composition", there is insufficient antecedent basis for this limitation since independent claim 28 recites "anionic liposomes." The Examiner states that this rejection can be overcome by amending the claim to recite "anionic liposomes."

Again, it unclear as to what the Examiner intends since independent claim 28 is directed to "A *therapeutic phospholipid composition* ..... wherein the composition comprises: a) *anionic liposomes*;..." and claim 29 is directed to "[t]he *phospholipid composition* of claim 28 wherein the concentration of *liposomes*....". Accordingly, in order to clarify the dependency and antecedent basis for claim 29, claim 29 has been amended to recite "[t]he <u>therapeutic</u> phospholipid composition of claim 28 wherein the concentration of <u>anionic</u> liposomes....".

The Examiner further states that while claim 31 recites the limitation "wherein the concentration of liposomes...", there is insufficient antecedent basis for this limitation as independent claim 30 recites "anionic liposomes." Accordingly, claim 31 has been amended to recite "wherein the concentration of <u>anionic</u> liposomes..." In addition, claim 39 has also been amended to recite "<u>anionic</u> liposomes." The Examiner points out that this amendment should also be made to claim 44, however, claim 44 has been withdrawn as a result of the restriction requirement.

The Examiner maintains that there is insufficient antecedent basis for the limitation "wherein the *biological membrane*" in dependent claim 32. However, claim 32 depends from claim 31, which in-turn depends from independent claim 30. Independent claim 30 does expressly include the phrase "through a biological membrane...". Therefore, it is unclear as to the Examiner's basis for this rejection of claim 32.

Claim 34 has been amended to recite "[t]he composition of claim 31..." rather than "the phospholipid composition....." .

Claims 25 and 37 have been amended to clarify that the composition may contain any one of the peptides of SEQ ID Nos. 3-6.

In summary, based upon these amendments to the claims, the Examiner's rejections under 35 U.S.C. 112, first and second paragraphs, have been overcome and should be withdrawn. No new matter is introduced as a result of these amendments. Applicants have amended their claims to more clearly define the instant invention and not to avoid cited art in the Examiner's rejections.

Rejections Under 35 U.S.C. §102(b)

The Examiner has rejected claims 40-42 under 35 U.S.C. 102(b) as being anticipated by O'Brien et al (WO 9503821 A1). In making this rejection, the Examiner maintains that O'Brien et al. teach a saposin C sequence that is 100% identical to SEQ ID Nos. 1 and 2 of the present application, and that these sequences are described by the formulas of SEQ ID Nos. 2-6 of O'Brien. Per the Examiner's suggestion, claims 40-42 have been amended to add the additional term "consisting of" to these claims. The Applicants respectfully submit that these amendments made herein address and overcome this rejection of claims 40-42 based upon 35 U.S.C. §102(b), and request that this rejection be withdrawn.

The Examiner has rejected claims 16-37 and 40-44 under 35 U.S.C. 102(b) as being anticipated by Vaccaro et al (IDS No. 30). In making this rejection, the Examiner argues that Vaccaro et al. teach that saposin C promotes fusion of PS-liposomes in a pH-dependent manner, thereby introducing saposin C into the class of fusogenic peptides and that the fusogenic behavior occurs at a lower pH (regarding claims 18, 30 and 38). The Examiner also argues that Vaccaro et al. teach a liposomal composition containing saposin C and glycoceramidase, the later of which is known for the treatment of Gaucher's disease. The Applicant respectfully traverses this rejection, as Vaccaro et al. fails to disclose each element of the claimed invention.

As an initial matter, claims 43 and 44 have been withdrawn as a result of a restriction requirement and as such, the rejection of these claims is moot. If the Examiner would like to include claims 43 and 44 in the prosecution of this application, the Applicant would certainly be receptive to doing that.

Vaccaro et al. discloses a composition containing saposin C, PS (phosphatidylserine) liposomes and glucosylceramidase, in an acetate buffer (page 182, column 1). Vaccaro et al. does not disclose each element of the present invention. In particular, the claims of the present invention require a "safe and effective amount of a pharmaceutical agent contained within the phospholipids." Vaccaro et al. does not disclose or suggest the use of a pharmaceutical agent contained within phospholipids. Therefore, since Vaccaro et al. does not teach all limitations required by the claims that define the present invention, the Examiner's rejection under 35 U.S.C. §102(b) has been overcome and should be withdrawn.

Rejections Under 35 U.S.C. §103(a)

The Examiner has rejected claims 16-25, 29-31 and 33-42 under 35 U.S.C. 103(a) as being unpatentable over Vaccaro et al., in view of Gross (USP 5,766,626) and O'Brien et al. (WO 9503821 A1). In making this rejection, the Examiner argues that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute the fusogenic peptide taught by Gross for the fusogenic peptide of Saposin taught by Vaccaro et al. and that a person of ordinary skill in the art would have been motivated to make this substitution as Gross demonstrates the effectiveness of using a fusogenic peptide for the delivery of a pharmaceutical agent. The Examiner further maintains that a person of ordinary skill in the art would have expected success in making the above substitutions as Vaccaro

et al. demonstrated the fusogenic activity of Saposin C and the conditions that favor that activity and accordingly, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and as a whole was *prima facie* obvious. The Applicant respectfully traverses this rejection.

As an initial matter, O'Brien et al. *does not* teach a saposin C sequence that is 100% identical to SEQ ID Nos. 1 and 2 of the present invention which are described by the formulas of SEQ ID Nos. 2-6 of O'Brien et al. (regarding claims 23-25, 37, and 40-42). Moreover, claims 40-42, which are directed to the Saposin C sequences, have been amended to add the language "consisting of" to more clearly define the peptide sequences.

Vaccaro et al. is directed to saposin C-induced fusion of phosphatidylserine-containing vesicles. Vaccaro et al. also discuss the pH-dependent fusion of such vesicles. Nowhere does Vaccaro et al. teach, suggest or motivate one skilled in the art to use the Saposin C/phosphatidylserine system for delivery of a pharmaceutical agent using a membrane-fusion mechanism. The focus of the Vaccaro et al publication was an examination of saposin C-induced changes in artificial lipid model systems.

Gross (USP 5,766,626) is directed to a lipid vesicle composition for use in delivering a vesicle-encapsulated agent to a target cell. The composition may include a fusion protein to promote fusion of vesicles to the target cells. Gross specifically discloses and claims an isoform of the protein glyceraldehyde-3-phosphate dehydrogenase, N-methylmaleimide-sensitive fusion proteins, viral fusion proteins and fragments thereof, to facilitate fusion of lipid vesicles. Gross does not teach, suggest or motivate one skilled in the art to use the Saposin C or related glycoproteins.

The Examiner has incorrectly drawn an analogy between Saposin C and the proteins cited in Gross, such as the isoform of glyceraldehyde-3-phosphate dehydrogenase. Saposin C is a heat-stable sphingolipid activator glycoprotein or coenzyme (see present application, paragraph 0008) and it may also be characterized as an extracellular fibrous/structural protein. In contrast, glyceraldehyde-3-phosphate dehydrogenase is an intracellular enzymatic protein which primarily serves to catalyze the oxidative phosphorylation of its aldehyde substrate. Accordingly, in both structure and function, these are two very different proteins with very different functions. Each of these two proteins will have different physio-chemical mechanisms for interacting with the biological membrane environments and in-turn, the mechanisms by which these proteins facilitate the transport of active agents across biological membranes. Therefore, one skilled in the art would not substitute the protein of Vaccaro et al. or O'Brien for those in Gross to arrive at the present invention.

The Examiner has also rejected claims 26-28 and 43-44 under 35 U.S.C. §103(a) as being unpatentable over Vaccaro et al. and O'Brien as applied to claims 16-21 (above) and further in view of Okkels et al. (USPA 20020127219) and Qi (IDS reference no. 41). In making this rejection, the Examiner asserts that it would have been obvious for a person of ordinary skill in the art at the time the invention was made to use GCB polypeptide (or acid beta-glucosidase) for the treatment of Gaucher's disease using the composition taught by Gross and Vaccaro et al. Claims 26-28 are not directed to a treatment of Gaucher's disease and as such, it is not clear as to why these claims were included in this rejection. Nevertheless, claims 43-44 which are directed to a treatment of Gaucher's disease have been withdrawn as a

result of a restriction requirement, as being drawn to a non-elected invention. As such, the Examiner's rejection of these claims is moot.

In summary, the prior art references cited by the Examiner do not teach or suggest the present invention as claimed herein. Accordingly, the rejections under 35 U.S.C. § 103(a) have been overcome and should be withdrawn.

It is respectfully submitted that the amendments and remarks herein overcome the rejections made in the office action and that the present application is now in form for allowance. Accordingly, early reconsideration and allowance of the claims, as currently pending, are earnestly solicited.

Respectfully submitted,

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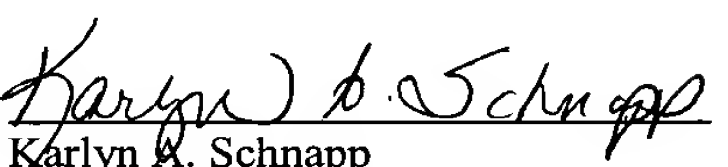
By 

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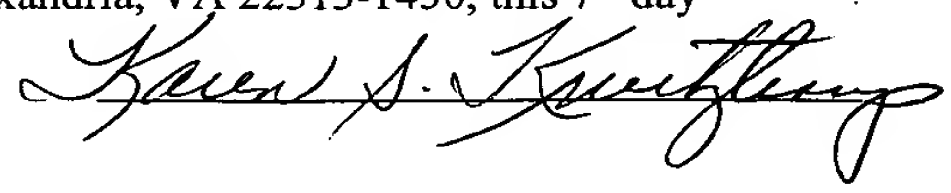

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